Adjuvants and Excipients

The Food Safety and Inspection Service (FSIS) has transferred the official responsibility to evaluate adjuvants and excipients used in Veterinary Biologics back to the Animal and Plant Health Inspection Service (APHIS). FSIS had been providing chemical, toxicological, and pathologic evaluations of new adjuvants/excipients, but APHIS now has the scientific resources necessary to conduct these evaluations. Resuming adjuvant reviews eliminates a step in the approval process that industry must follow and requires contact only with APHIS.

All new product licensing packages should include a thorough description and the composition of any adjuvants. Center for Veterinary Biologics (CVB) Notice 06-15, and Veterinary Services Memorandum 800.51 provide guidance regarding appropriate data that should be submitted for adjuvants. In general, **all** new product license applications should contain the following information:

1. Generic name of adjuvant (and Trade Name if applicable)
2. Chemical composition of adjuvant (list all ingredients and proportions).
3. Amount of completed/total adjuvant per dose of product
4. Dose volume of product
5. Animal species in which the product is to be used
6. Route of administration (and specific anatomical site, if designated)
7. Information regarding source, grade, quality of tests performed (if any) on each lot
8. Slaughter withdrawal period proposed [at least 21 days is required as per 9 CFR 112.2(a)(8)]
9. Other products for which the adjuvant/excipient has been approved (if applicable)

Initial Reviewer Evaluation

Reviewers should compare the additive description and composition with historic data regarding adjuvants and excipients on file at the CVB. A spreadsheet containing approved adjuvants is available to facilitate review of historic data (see adjuvant spreadsheet) The spreadsheet contains information regarding adjuvants and miscellaneous additives that have been approved for use by the CVB. Please note that not all of the products that these approved additives are to be used in are currently licensed. Some products are in the pre-license stage. Some products listed have been licensed but may not be currently manufactured. The adjuvant spreadsheet may not contain all of the adjuvants approved by the CVB. It is simply meant to be used as a tool for reviewers to use when reviewing adjuvant submissions. Reviewers are encouraged to contact the Policy Evaluation and Licensing Intranet Coordinator if revisions or updates to this spreadsheet are identified. Additional data regarding previously approved adjuvants are filed in the adjuvant folder for each firm, located in the file room. If the proposed adjuvant formulation (content, quantity per dose) and associated final use product is sufficiently similar to previously approved formulations, the historical data on file, in addition to satisfactory field safety trial results, may be adequate to approve the

adjuvant in the new product. Any adjuvant may be reevaluated, however, if field safety trial results indicate this is warranted.

Additional data and evaluation may be required for previously approved adjuvants that are to be included in products in unique ways. The reviewer should consult with the adjuvant coordinated review team (CRT) if any questions arise regarding adjuvants. The purpose of the adjuvant CRT is to generate useful and timely information for the reviewer in order to facilitate scientific review of adjuvants. In order to achieve this purpose, goals of the adjuvant CRT include:

1. The CRT will strive to provide a response to adjuvant-related questions within 4 weeks of initial consultation.
2. The pathologist on the adjuvant CRT is also available for specific questions related to pathology at any time. [redacted]

The reviewer should always consult with the adjuvant CRT prior to approval of new adjuvants, or to approval of previously approved adjuvants to be used at increased levels, in different routes of administration, or with different withdrawal periods. Results of an injection site study in the host animal may be required to complete evaluation of the adjuvant.

<u>Considerations for an injection site study</u>

The following guidelines should be considered when reviewing an injection site study:

1. A protocol should be submitted by the firm prior to conducting the study to ensure the study design is adequate. The proposed dates of conducting the study should be included to allow observation by CVB personnel if deemed necessary.

2. At least 10 animals of the minimum age should be included for adjuvants used in food-producing species other than fish and poultry:
    a. The firm should compare the injection site of the new adjuvant to a previously approved product by injecting the new product on one side of the animal, and the placebo on the other side of the animal. [redacted]
    b. The injection sites should be examined grossly by a veterinarian or board certified veterinary pathologist. The veterinarian or veterinary pathologist should also collect the tissues to be analyzed histopathologically. The results of gross pathologic examination should be included in the report. High resolution pictures of any gross pathology should be included.
    c. Histopathology of tissue samples taken should be analyzed by a board certified veterinary pathologist who has no knowledge regarding the products used in the study, and photographs of the histopathologic sections of the injection site should be included in the final report. The histological evaluation is conducted to evaluate and ensure that the local

inflammatory response is consistent with the expected physiological/immunological response to foreign material in the respective tissue. Observations that are inconsistent with the expected process may require additional evaluation.

3. At least 10 birds of minimum age of the species the product is to be used in should be included for adjuvants to be used in poultry.

4. At least 20 fish of minimum age/size of the species the product is to be used in should be included for injection site studies in aquatic species meant for human consumption. The study may be done using the same dose as per label recommendations, or at double the dose recommended on the label.
    a. Many adjuvants cause some degree of tissue adhesion and pigmentation in the abdominal cavity when administered intraperitoneally. The Speilberg Scoring System, based on the size and density of the adhesion, should be used to analyze data from aquatic species. This scoring system is described in the article, *Experimental studies on the efficacy and side-effects of intraperitoneal vaccination of Atlantic salmon (Salmo salar L.) against furunculosis,* by Midtylyng, et al, in "Fish and Shellfish Immunology (1996) 6, 335-350. The study should be evaluated for degree of tissue pigmentation and adhesion in the abdominal cavity, as well as vaccine residues in the abdominal cavity. Speilberg scores of 3 or less are acceptable. Speilberg scores of 4 or greater are likely to be noticed by laymen during evisceration and may leave damage to the carcass after evisceration.
    b. Vaccine residues in edible portions of fish present at slaughter are not acceptable.

5. For non-food producing animals like dogs and cats, the results of an acceptable field safety study are adequate to demonstrate safety of the adjuvant.

Additional information that may be considered as supporting data in an injection site study report include:

1. Summary of any available studies (i.e., peer reviewed publications, relevant internal reports) that contain pathologic assessments of the experimental product when administered to the target species
2. Data showing the time required for the resolution of any injection site reactions
3. For live organisms, a summary of any available data regarding clearance of the organism from the target species
4. Results of safety studies in laboratory animals like mice and guinea pigs

Additional considerations for novel adjuvants/excipients

For new adjuvants that are unique and have not been included in previously approved veterinary biological products, the following information may be required.

1. Toxicological Profile which should include
    a. Any information relative to the listing of the additives on lists of approved additives (i.e. Generally Regarded as Safe (GRAS), Annex II, Drinking Water Standards, etc.). Provide a copy of the Material Safety Data Sheet (MSDS) or reference the MSDS number for each additive (if available)
    b. Results of toxicological studies to determine the local and or systemic effects of the additive on laboratory animals.
    c. Summary of any oral/acute testing of the additives in target and non-target species.
    d. Summary of any information regarding how additives are metabolized by the target animal
    e. Information regarding the carcinogenicity of the additives
    f. Known reactivity of each additive.
    g. Known pharmacological activity of each additive

2. Human Exposure Profile
    a. Estimate of the total volume/mass of the additives that will be administered to the target animal under the proposed label indication
    b. Estimate of the human consumption/exposure to each additive
    c. Measurements of the levels of residue in tissue at proposed withdrawal period to make sure the levels are not over Food and Drug Administration (FDA) tolerances for food if available
    d. FDA tolerance established for additive and cite source if available

Exceptions to Slaughter Withdrawal Period Requirements

No slaughter withdrawal statement is needed for a non-injectable (i.e. oral, intranasal, immersion, etc.) product clearly labeled solely for neonatal animals because they do not enter the food chain.

Non-injectable biologics used for food producing animals entering the food chain must have a slaughter withdrawal period of not less than 21 days, as per 9 CFR 112.2(a)(8).

[redacted]

CVB Response to Adjuvant/Excipient Submissions

Based on the data requested, the CVB will make a determination regarding the suitability of the adjuvant. The assessment may be:

1. Withholding period not necessary

2. Minimum withholding period of 21 days is appropriate
3. Longer withholding period is appropriate
4. Additional data required

The CVB response should also include a summary of the rationale used to make the determination regarding the suitability of the adjuvant. The adjuvant spreadsheet manager should be cc'ed on outgoing correspondence related to adjuvant approvals to ensure the adjuvant spreadsheet is kept up-to-date.

An adjuvant folder is created for each establishment. The folder is located behind the General Correspondence folder for each establishment [redacted] Any documents related specifically to adjuvants should be labeled by the reviewer in the upper right hand corner of the hard copy of the outgoing letter forwarded to the program assistant. These documents should be marked as "Adjuvant," in red ink. The program assistant should write "Adjuvant," in red ink on the yellow copy of the outgoing letter. Any correspondence labeled as such should be filed in the adjuvant folder for the firm, and not in the #1 file.

Reviewers should attempt to separate adjuvant items that may be part of a larger submission. If possible, a separate response should be prepared to address adjuvant issues. This will facilitate the separation of adjuvant-related documents from items that should be filed in the #1 file for a product.

The reviewers performing first-level review of outgoing correspondence should check to make sure that the reviewer-author has marked his/her letters appropriately.

Applicable documents that have recently been forwarded from FSIS, or other miscellaneous adjuvant approval information should also be labeled as "Adjuvant" in red ink in the upper left hand corner of the first page of the document, along with the establishment number of the applicable firm. These documents should be forwarded to the file room and will also be placed in the adjuvant folder for the applicable firm.